



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, 15/62, C07K 14/78, 19/00, C12N 15/861, 15/867, A61K 48/00, G01N 33/68	A1	(11) International Publication Number: WO 00/68379 (43) International Publication Date: 16 November 2000 (16.11.00)
(21) International Application Number: PCT/US00/12392 (22) International Filing Date: 5 May 2000 (05.05.00) (30) Priority Data: 60/133,243 7 May 1999 (07.05.99) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/133,243 (CON) Filed on 7 May 1999 (07.05.99) (71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LIBUTTI, Steven, K. [US/US]; 14013 Welland Terrace, North Potomac, MD		20878 (US). FELDMAN, Andrew [US/US]; 7713 Greenbrook Drive, Greenbelt, MD 20770 (US). (74) Agents: SPRATT, Gwendolyn, D. et al.; Needle & Rosenberg, P.C., 127 Peachtree Street, N.E., Atlanta, GA 30303-1811 (US). (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: METHODS FOR TREATING TUMORS USING ANTIANGIOGENIC COMPOUNDS (57) Abstract <p>This invention provides a compound comprising a recombinant nucleic acid encoding an antiangiogenic protein inserted within a viral nucleic acid, wherein the recombinant nucleic acid can be packaged in a virus particle and wherein expression of the recombinant nucleic acid encoding the antiangiogenic protein results in production of the antiangiogenic protein. The present invention also provides a method of delivering an antiangiogenic protein to a cell, delivering an antiangiogenic protein to a subject, and treating a tumor in a subject comprising administering a virus comprising a recombinant nucleic acid encoding an antiangiogenic protein inserted within the viral nucleic acid, wherein the recombinant nucleic acid can be packaged in a virus particle, and wherein expression of the recombinant nucleic acid encoding the antiangiogenic protein results in production of the antiangiogenic protein, thereby delivering the antiangiogenic protein to the cell.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZV	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/12392

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/12 C12N15/62 C07K14/78 C07K19/00 C12N15/861 C12N15/867 A61K48/00 G01N33/68		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K A61K G01N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 49321 A (LI HONG; LU HE; RAGOT THIERRY; YEH PATRICE; GRISCELLI FRANC; LEGRAND YV) 5 November 1998 (1998-11-05)	1-5, 8, 11, 16-20, 23-37
Y	page 2, line 17, paragraph -page 3, line 11 page 8, line 12 - line 23 page 11, line 22 -page 13, line 33 <div style="text-align: center;">-/-</div>	6, 9, 10, 13-15
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*&* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">24 August 2000</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">11/09/2000</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Mandl, B</div>

INTERNATIONAL SEARCH REPORT

In International Application No

PCT/US 00/12392

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANAKA T. ET AL.: "VIRAL VECTOR-TARGETED ANTIANGIOGENIC GENE THERAPY UTILIZING AN ANGIOSTATIN COMPLEMENTARY DNA" CANCER RESEARCH, vol. 58, no. 15, 1 August 1998 (1998-08-01), pages 3362-3369, XP000857409 ISSN: 0008-5472	1-3, 8, 16-20, 23-37
Y	the whole document	21, 22, 38, 39
Y	WO 98 48834 A (SINAI SCHOOL MEDICINE ; NAT INST HEALTH (US)) 5 November 1998 (1998-11-05) page 17, line 11 - line 21	21, 22, 38, 39
X	BRAMSON J. L. ET AL.: "Direct intratumoral injection of an adenovirus expressing Interleukin-12 induces regression and long-lasting immunity that is associated with highly localized expression of Interleukin-12" HUMAN GENE THERAPY, vol. 7, 20 October 1996 (1996-10-20), pages 1995-2002, XP002093895 ISSN: 1043-0342	1, 2, 11, 16, 18, 23-31
X	CRYSTAL R. G. : "The body as manufacturer of endostatin." NATURE BIOTECHNOLOGY, vol. 17, April 1999 (1999-04), pages 336-337, XP002145429 cited in the application the whole document	1-5, 8, 12, 16-19, 23-31
X	TANAKA T. ET AL.: "Viral vector-mediated transduction of a modified platelet factor 4 cDNA inhibits angiogenesis and tumor growth." NATURE MEDICINE, vol. 3, no. 4, 1997, pages 437-442, XP002145430 ISSN: 1078-8956 the whole document	1-3, 5, 8, 12, 16-20, 23-31, 37
	— -/-	

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 00/12392

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BLEZINGER P. ET AL.: "SYSTEMIC INHIBITION OF TUMOR GROWTH AND TUMOR METASTASES BY INTRAMUSCULAR ADMINISTRATION OF THE ENDOSTATIN GENE" NATURE BIOTECHNOLOGY, vol. 17, no. 4, April 1999 (1999-04), pages 343-348, XP000857410 ISSN: 1087-0156 cited in the application	37
Y	the whole document	1-5,8, 16-20, 23-36
X	WO 97 16169 A (CHIRON CORP) 9 May 1997 (1997-05-09)	37
Y	the whole document	1-5,8, 16-20, 23-36
Y	SCHWARZ M. ET AL.: "EMAP II: A modulator of neovascularization in the developing lung." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 20, no. 2, February 1999 (1999-02), pages L365-L375, XP002145431 ISSN: 1081-5589 the whole document	6
Y	PIKE S. E. ET AL.: "Vasostatin, a calreticulin fragment, inhibits angiogenesis and suppresses tumor growth." JOURNAL OF EXPERIMENTAL MEDICINE, vol. 188, no. 12, 21 December 1998 (1998-12-21), pages 2349-2356, XP002145432 ISSN: 0022-1007 column W	9
Y	WO 97 34586 A (TSIARAS WILLIAM G ;SPEAR PETER D (US); BAETGE E EDWARD (US); CYTOT) 25 September 1997 (1997-09-25) page 9, paragraph 2	10
Y	SHUTTLEWORTH C. A.: "Type VIII collagen." INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY, vol. 29, no. 10, October 1997 (1997-10), pages 1145-1148, XP000938722 ISSN: 1357-2725 the whole document	13
	-/-	

INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/US 00/12392

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>RAMCHANDRAN R. ET AL.: "Antiangiogenic activity of restin, NC10 domain of human collagen XV: Comparison to endostatin." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 255, no. 3, 24 February 1999 (1999-02-24), pages 735-739, XP002145434 ISSN: 0006-291X the whole document</p>	14
Y	<p>RAMCHANDRAN R. ET AL.: "Cloning, expression of a novel anti-angiogenic protein: Restatin." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 40, March 1999 (1999-03), page 620 XP000938553 ISSN: 0197-016X the whole document</p>	15
P,X	<p>SAUTER B. V. ET AL.: "Adenovirus-mediated gene transfer of endostatin in vivo results in high level of transgene expression and inhibition of tumor growth and metastases." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 9, 25 April 2000 (2000-04-25), pages 4802-4807, XP002145436 April 25, 2000 ISSN: 0027-8424 the whole document</p>	1,2,4, 16,18, 20, 23-31,37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/12392

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9849321	A	05-11-1998	AU 7909698 A CN 1254378 T EP 0979290 A NO 995242 A ZA 9803553 A	24-11-1998 24-05-2000 16-02-2000 27-12-1999 04-02-1999
WO 9848834	A	05-11-1998	AU 7471098 A	24-11-1998
WO 9716169	A	09-05-1997	AU 7525296 A AU 7527596 A EP 0858322 A WO 9716170 A	22-05-1997 22-05-1997 19-08-1998 09-05-1997
WO 9734586	A	25-09-1997	US 5904144 A AU 716400 B AU 2541997 A EP 0927024 A JP 2000507854 T	18-05-1999 24-02-2000 10-10-1997 07-07-1999 27-06-2000